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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07D 223/16, 217/24, 209/34
A61K 31/55

A1

(11) International Publication Number: WO 93/16997

(43) International Publication Date: 2 September 1993 (02.09.93)

(21) International Application Number: PCT/US93/01425

(22) International Filing Date: 23 February 1993 (23.02.93)

(30) Priority data:
07/841,603 25 February 1992 (25.02.92) US

(60) Parent Application or Grant
(63) Related by Continuation
US 07/841,603 (CIP)
Filed on 25 February 1992 (25.02.92)

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(81) Designated States: AU, BB, BG, BR, CA, CZ, FI, HU, JP, KR, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).

Published
With international search report.

(54) Title: 2,3,4,5-TETRAHYDRO-1H-3-BENZAZEPINES HAVING ANTI-PSYCHOTIC ACTIVITY, AND SYNTHESIS OF α-SUBSTITUTED-ARYLACETAMIDES

(57) Abstract

A novel process for the preparation of α-substituted arylacetamides wherein the substituent is an aromatic group or a 1-alkenyl or 1-cycloalkenyl group and wherein the nitrogen atom carries no hydrogen atoms comprises the reaction of an arylacetamide having one or two hydrogen atoms on the α-carbon atom, wherein the nitrogen atom carries no hydrogen atoms, with a strong base in an inert aprotic organic solvent, followed by reaction with a zerovalent transition metal catalyst and then with a compound of the formula R^4-X, wherein R^4 is selected from aromatic groups, 1-alkenyl groups and 1-cycloalkenyl groups and X is a particular leaving group, especially a triflate group. The α-substituted arylacetamides are useful as intermediates in the preparation (by reduction) of α-substituted arylethylamines, e.g., 1-substituted-2,3,4,5-tetrahydro-1H-3-benzazepines, having pharmacological activity. Certain benzazepines wherein the 1-substituent R^4 is 1-(1-cycloalkenyl) are novel.

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2,3,4,5-TETRAHYDRO-1H-3-BENZAZEPINES HAVING ANTI-PSYCHOTIC ACTIVITY, AND SYNTHESIS OF α-SUBSTITUTED-ARYLACETAMIDES

BACKGROUND OF THE INVENTION

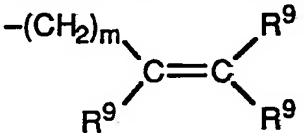
This invention relates to 2,3,4,5-tetrahydro-1H-3-benzazepines having anti-psychotic activity, and also to the synthesis of α-substituted-arylacetamides, especially fused-ring nitrogen heterocycles, in particular dihydroindoles, 1,2,3,4-tetrahydroisoquinolines and 1,2,3,4,5,6-hexahydro-3-benzazocines, and most particularly 2,3,4,5-tetrahydro-1H-3-benzazepines.

Dihydroindoles, 1,2,3,4-tetrahydroisoquinolines, 1,2,3,4,5,6-hexahydro-3-benzazocines, and particularly 2,3,4,5-tetrahydro-1H-3-benzazepines are known to have useful pharmacological properties. For example, U. S. Patents 3,393,192, 3,609,138, 4,011,319, 4,284,555 and 4,477,378, and British Patent Specification no. 1,118,688, all describe 1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepines having various activities described as antibacterial effects, central nervous system effects and hypotensive effects.

Weinstock *et al.* in *Drugs of the Future*, Vol. 10, No. 8, pp. 645-697 (1985) discuss the profound effect that 1-phenyl substituents have on the dopaminergic activity of certain types of benzazepines; see in particular Table II on page 666.

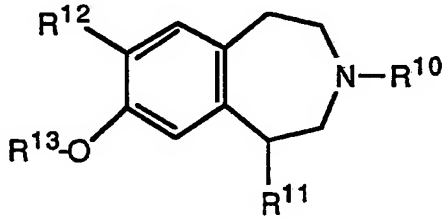
European Patent Application No. 83105610.6 (published as 0 096 838) discloses certain 1-aryloxy-2,3,4,5-tetrahydro-1H-3-benzazepines optionally having alkoxy substituents in the 7- and/or 8-position; these compounds are disclosed as having utility in treating depression.

U. S. Patent 5,015,639 describes and claims 2,3,4,5-tetrahydro-1H-3-benzazepines lacking a 1-phenyl group but having instead a variety of 1-substituents including a group of the formula



wherein m is 0 or 1, and each of the groups R^9, which can be the same or different, is a hydrogen atom or an alkyl, alkoxy, alkoxyalkyl, aralkyl or aryl group. These compounds have good anti-dopaminergic activity, and in particular show surprising selectivity for the D-1 subclassification of dopaminergic receptors. Iorio *et al.*, *Pharmacol. Exp. Ther.* (1983), 226, page 462, and Iorio et al. in *Neurobiology of Central D_1-Dopamine Receptors*, pages 1-14 in Advances in Experimental Medicine and Biology 204, Eds. Creese and Breese, Plenum, New York, 1986, have also evaluated the effects of benzazepines on dopamine receptors. Charifson *et al.*, J. Med. Chem. (1988), 31, pages 1941-1946, have similarly evaluated 1,2,3,4-tetrahydroisoquinolines.

International Application No. PCT/US 91/04046 describes and claims (inter alia) compounds having the structural formula A



A

and the pharmaceutically acceptable salts thereof, wherein:
R^{10} represents H, C_{1-4}–alkyl, allyl or cyclopropylmethyl;
R^{11} represents C_{3-8}–cycloalkyl or C_{5-8}–cycloalkenyl;
R^{12} represents C_{1-4}–alkyl; and
R^{13} represents (inter alia) R^{12}, H or $R^{12}CO$.

These compounds are useful in the treatment of psychoses, depression, pain and hypertension.

Ciufolini *et al.*, *Tetrahedron Letters* **1987**, Vol. 28 No. 2, 171-174, have described a 'model' intramolecular arylation of 2-[2-(2-iodophenyl)ethyl]-indane-1,3-dione with tetrakis(triphenylphosphine)-palladium(0), to yield a spiro(indane-1,3-dione-2,1'-indane), in experiments on the synthesis of Friedricamycin. In further studies of prototype substrates and also of substrates used in studies of the synthesis of Friedricamycin, Ciufolini *et al.*, *J. Org. Chem. [Communications]* **1988**, *53*, 4149-4151, have described intramolecular arylations of 'soft' enolates (*i.e.*, enolates having a pK_a <15) catalyzed by zerovalent palladium. A phenyl halide moiety in one part of the molecule was condensed with an enol in another part of the molecule to provide a benzo-fused five- or six-membered homocyclic or heterocyclic ring; but compounds with a fused four-membered ring could not be produced. One example in Table I therein shows the formation of an indolone by intramolecular condensation of an N-methyl-N-(2-ethoxycarbonylpropanoyl)-2-iodoanilide. In an adaptation of this method, Piers *et al.*, *J. Org. Chem.* **1990**, *55*, 3454-3455, have disclosed a five-membered ring annulation method based on Pd(0)-catalyzed intramolecular coupling of a vinyl iodide function with an enolate anion function; in this method, the enolate anion was in a saturated five- or six-membered ring.

A modification of the reaction disclosed by Ciufolini *et al.* was published by Negishi *et al.*, *J. Am. Chem. Soc.*, **1989**, *111*, 8018-8020. Using compounds analogous to those which, in the hands of Ciufolini *et al.*, had failed to produce compounds with a fused four-membered ring, they were able to effect a cyclization in the presence of carbon monoxide under pressure: the product was a ketone with its carbonyl group (provided by the carbon monoxide) in a fused five-membered ring. They were similarly able to produce analogous ketones with the carbonyl group in a fused six- or seven-membered ring, and even effect the cyclization on non-cyclic intermediates to produce unfused cyclopentenones.

In all these reactions catalyzed by a zerovalent metal, the enolate is generally stabilized by an adjacent activating group (such as ester-carbonyl, keto-carbonyl or nitrile).

SUMMARY OF THE INVENTION

In its broadest aspect the present invention provides a novel process for the preparation of α-substituted arylacetamides wherein the substituent is an aromatic group or a 1-alkenyl or 1-cycloalkenyl group and wherein the nitrogen atom carries no hydrogen atoms;

which comprises the reaction of an arylacetamide having at least one hydrogen atom and preferably two hydrogen atoms on the α-carbon atom, wherein the nitrogen atom carries no hydrogen atoms, with a strong base in an inert aprotic organic solvent;

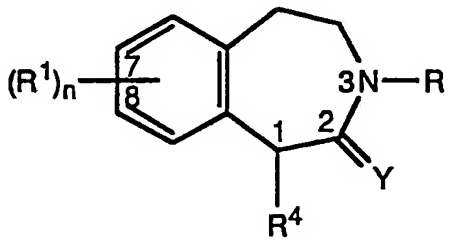
followed by reaction, in the presence of a zerovalent transition metal catalyst, with a compound of the formula

R^4–X (I),

wherein R^4 is selected from aromatic groups, 1-alkenyl groups and 1-cycloalkenyl groups;

and X is a leaving group, e.g., —OSO_2F or an activated ester group.

The invention further provides novel 1,3,4,5-tetrahydro-2H-3-benzazepines and 2,3,4,5-tetrahydro-1H-3-benzazepines of the formula



(II);

wherein n is 0, 1, 2, 3 or 4;

each R^1 is independently selected from alkenyl, alkoxy, hydroxy, alkenyloxy, cycloalkyl, nitro, halogen, polyfluoroloweralkyl, phenyl and phenoxy, or two groups R^1 in adjacent positions optionally form an alkylenedioxy group or a fused benzene ring, and the phenyl or phenoxy group or the fused benzene ring is optionally substituted by a group selected from alkyl, alkenyl, alkoxy, hydroxy, alkenyloxy, cycloalkyl, nitro, halogen, polyfluoroloweralkyl, and alkylenedioxy;

R^4 is a 1-cycloalkenyl group;

R is an alkyl, alkenyl, aryl, aralkyl, cycloalkyl or cycloalkylalkyl group; and Y is an oxygen atom or H_2;

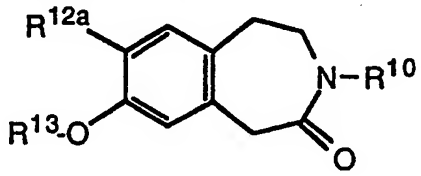
and their non-toxic salts with bases when R^1 is or contains a hydroxy group;

and their non-toxic acid addition salts when Y is H_2.

DETAILED DESCRIPTION OF THE INVENTION

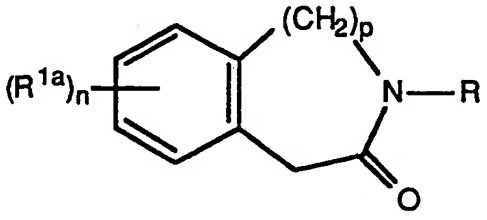
It should in particular be noted that the process of the present invention does not require the arylacetamide to have two powerful activating groups (such as ester-carbonyl, keto-carbonyl or nitrile) substituting the α-carbon atom.

The arylacetamide used as starting material can be prepared by standard methods that are well known to those skilled in the art. For example, International Application No. PCT/US 91/04046, the disclosure of which is incorporated herein by reference, describes the preparation of 1,3,4,5-tetrahydro-2H-benzazepin-2-ones of the formula



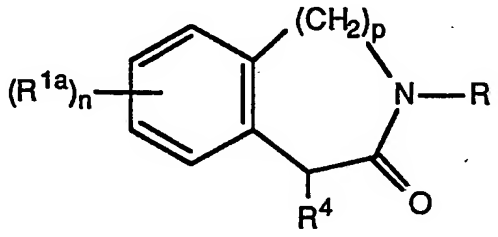
wherein R^{10} and R^{13} are as defined above, and R^{12a} is R^{12} as defined above or a hydrogen or halogen atom. These compounds can be used as starting materials in the process of the present invention.

The arylacetamide is preferably α-unsubstituted and in particular its amide function preferably forms a fused ring with the aryl group, as in a 3-unsubstituted 1,3-dihydro-2H-indol-2-one, 4-unsubstituted 1,2,3,4-tetrahydro-isoquinolin-3-one, 1-unsubstituted 1,3,4,5-tetrahydro-2H-3-benzazepin-2-one or 1-unsubstituted 1,2,3,4,5,6-hexahydro-3-benzazocin-2-one. So the arylacetamide preferably has the formula:



(III),

and the 3-substituted 1,3-dihydro-2H-indol-2-one, 4-substituted 1,2,3,4-tetrahydro-isoquinolin-3-one, 1-substituted 1,3,4,5-tetrahydro-2H-3-benzazepin-2-one or 1-substituted 1,2,3,4,5,6-hexahydro-3-benzazocin-2-one prepared therefrom preferably has the formula



(IV);

wherein p is 0, 1, 2 or 3 (but preferably 2, as in a 1,3,4,5-tetrahydro-2H-3-benzazepin-2-one);

n is 0, 1, 2, 3 or 4 (but preferably 1 or 2);

each R^{1a} is independently selected from alkyl, alkenyl, alkoxy, alkenyloxy, cycloalkyl, nitro, halogen, polyfluoroloweralkyl, phenyl and phenoxy, or two groups R^{1a} in adjacent positions optionally form an alkylenedioxy group or a fused benzene ring, and the phenyl or phenoxy group or the fused benzene ring is optionally substituted by a group selected from alkyl, alkenyl, alkoxy, alkenyloxy, cycloalkyl, nitro, halogen, polyfluoroloweralkyl, and alkylenedioxy;

R^4 is selected from aromatic groups, 1-alkenyl groups and 1-cycloalkenyl groups;

and R is an alkyl, alkenyl, aryl, aralkyl, cycloalkyl or cycloalkylalkyl group.

It should be noted that compounds of the formula II have an asymmetrically-substituted carbon atom at the 1-position and can exist in optically active forms. All such forms, whether racemic forms or optically active (chiral) forms are covered by the present invention. Similarly, compounds of the formula IV can exist as racemates or optically active forms.

These immediate products of the reaction, namely the α-substituted arylacetamides, can be used as intermediates in the preparation of α-substituted arylethylamines having pharmacological utility. For example, a compound of the formula II (wherein Y is O) or IV can be reduced; further optional steps may then be carried out to provide a compound

having pharmacological utility, such as the removal of a protecting alkyl (especially methyl) group from an alkoxy substituent. The (R)- and (S)-isomers can be separated if necessary at an appropriate point in the synthesis. The product, *e.g.*, a 1-substituted-2,3,4,5-tetrahydro-1H-3-benzazepine, will have potential pharmacological utility.

The aryl group of the arylacetamide can be any aryl group, for example a phenyl group or a polycyclic aromatic hydrocarbon group such as 1- or 2-naphthyl, 1-, 2- or 9-anthranyl, 1-, 2-, 3-, 4- or 5-phenanthryl, 4-, 5-, 6- or 7-indanyl, 5-, 6-, 7- or 8-[(1,2,3,4-tetrahydro)-naphthyl], or 1-, 2-, 3- or 4-fluorenyl, or an aromatic heterocyclic group such as 2- or 3-thienyl, 2- or 3-furyl, or such an aromatic heterocyclic group fused to a benzene ring. The aryl group can be substituted, for example by one to three groups selected independently from alkyl, alkenyl, alkoxy, alkenyloxy, nitro, halogen, trifluoromethyl, cyano, cycloalkyl, alkynyloxy, or phenyl or phenoxy, or two adjacent positions can be substituted by alkylenedioxy, and the phenyl or phenoxy group in this list can itself be substituted similarly by alkyl, alkenyl, alkoxy, alkenyloxy, nitro, halogen, trifluoromethyl, cyano, cycloalkyl, alkynyloxy, or alkylenedioxy.

When used herein the following radicals have the assigned meanings:

alkenyl (including the alkenyl portion of alkenyloxy) — represents a straight or branched hydrocarbon chain having at least one carbon-to-carbon double bond and having from 2 to 10, preferably from 2 to 6, carbon atoms; it should especially be noted that, when R^4 in the compound of the formula R^4X is an alkenyl group, the group X is attached to said alkenyl group at a carbon atom forming the carbon-carbon double bond;

alkynyl (especially the alkynyl portion of alkynyloxy) — represents a straight or branched hydrocarbon chain having at least one carbon-to-carbon triple bond and having from 2 to 10, preferably from 2 to 6, carbon atoms;

alkyl (including the alkyl portions of alkoxy, cycloalkylalkyl and aralkyl) — represents a straight or branched, saturated hydrocarbon chain having from 1 to 10 carbon atoms but preferably a lower alkyl group having from 1 to 6 carbon atoms;

alkylene (in particular the alkylene portion of alkylenedioxy) — represents a straight or branched, saturated hydrocarbon chain having from 1 to 6, preferably from 1 to 3, carbon atoms, with the two free valencies on the same carbon atom or on different ones;

aryl (including the aryl portion of aryloxy and aralkyl groups) — represents phenyl, substituted phenyl, 1-naphthyl, 2-naphthyl and indanyl;

cycloalkenyl — represents a carbocyclic group having from 5 to 8, preferably 5 or 6, carbon atoms and one, two or three carbon-to-carbon double bonds in the ring (but preferably only one), and optionally bearing one or two lower alkyl substituents; it should especially be noted that, when R^4 in the compound of the formula R^4X is a cycloalkenyl group, the group X is attached to said cycloalkenyl group at a carbon atom bearing a carbon-carbon double bond;

cycloalkyl (including the cycloalkyl portion of cycloalkylalkyl)— represents a saturated carbocyclic ring having from 3 to 8, preferably from 5 to 7 carbon atoms;

halogen — represents fluorine, chlorine, bromine and iodine;

aromatic heterocyclic (heteroaryl) — represents a cyclic group having at least one O, S and/or N interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclic group having from 2 to 14, preferably from 2 to 8, especially from 2 to 5, carbon atoms, e.g., 2-, 3- or 4-pyridyl, 2- or 3-furyl, 2- or 3-thienyl, 2-, 4- or 5-thiazolyl, 2-, 4- or 5-pyrimidinyl, 2-pyrazinyl, 3- or 4-pyridazinyl, 3-, 5- or 6-[1,2,4-triazinyl], 3-or 5-[1,2,4-thiadiazolyl], 2-, 3-, 4-, 5-, 6- or 7-benzofuranyl, 2-, 3-, 4-, 5-, 6- or 7-(1-substituted)-indolyl, 2-, 4- or 5-oxazolyl, etc. Preferred heteroaryl groups are 2-, 3- or 4-pyridyl, 2- or 3-furyl, 2-, 4- or 5-imidazolyl, and 7-(1-substituted)-indolyl (where the 1-substituent is for example methyl);

substituted phenyl — represents a phenyl group in which 1 to 3 hydrogen atoms thereof are replaced by the same or different substituents independently chosen from alkyl, alkenyl, alkoxy, alkenyloxy, nitro, halogen, trifluoromethyl, cyano, cycloalkyl, alkynyloxy, or wherein two hydrogen atoms in adjacent positions are selected from alkylenedioxy;

polyfluoroloweralkyl — represents a straight or branched alkyl group containing 1 to 4 carbon atoms wherein at least two hydrogen atoms have

been replaced by fluorine atoms, e.g., C_2F_5, CH_3CF_2, and CF_3CH_2, and especially CF_3.

Certain compounds of the invention, i.e., those of the formula II wherein Y is H_2, are basic and form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for such salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those skilled in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with one equivalent of a suitable dilute aqueous base solution such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia or sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the salts are otherwise equivalent to their respective free base forms for purposes of this invention.

Certain compounds of the invention, i.e., those of the formula II wherein R^1 is, or contains, a hydroxy group, are phenolic and therefore acidic in nature. These compounds may form pharmaceutically acceptable salts with strong bases. Examples of such salts are the sodium, potassium and calcium salts. These salts are prepared by contacting the phenol with a sufficient amount of the appropriate base to produce a salt in the conventional manner. The free phenol may be regenerated by treating the salt with one equivalent of a suitable dilute aqueous organic acid solution, e.g., acetic acid or aqueous-alcoholic hydrochloric acid.

The group X of the compound of the formula I (R^4—X) is preferably an activated ester group, e.g. a sulfonate ester group such as triflate (trifluoromethane sulfonate), tosylate or mesylate. It can also be a group of the formula —OSO_2F. However, the reaction has failed with halogen atoms, even with iodine, as leaving group.

Several appropriate zerovalent transition metal catalysts are commercially available and can be used in the process of the present invention. In these catalysts, the metal itself is preferably palladium,

although nickel also works well in this type of reaction. When the transition metal is palladium or nickel, the catalyst will have the formula $M[L]_4$, wherein M is palladium or nickel and L is the ligand. L is preferably a trisubstituted phosphine, in particular a triarylphosphine wherein the aryl group is phenyl or even a heteroaryl group such as furanyl-2. Although L in the compound of the formula $M[L]_4$ can be a trialkylphosphine such as trimethylphosphine or triethylphosphine, the relative instability of these trialkylphosphine compounds — they tend to be pyrophoric — makes them less desirable.

Preferred palladium-containing or nickel-containing catalysts include tetrakis(triphenylphosphine)-palladium(0), tetrakis(triphenylphosphine)-nickel(0), tetrakis[tri(furanyl-2)phosphine]-palladium(0), tetrakis[tri(furanyl-2)]phosphine)-nickel(0), and tris(dibenzylideneacetonyl)bis-palladium(0) (which is sometimes designated $Pd_2(DBA)_3$). Of these, tetrakis(triphenylphosphine)-palladium(0) is especially preferred for reasons of cost, commercial availability, convenience of use, and efficacy. If necessary, it can be prepared by reaction of $PdCl_2$ with triphenylphosphine under reduction, e.g., with n-butyllithium. Palladium catalysts of this type that are not commercially available can be prepared by known methods; for example, from $Pd_2(DBA)_3$ and the phosphine.

The compound of the formula I is preferably used in a small excess over the compound of the formula III, e.g., 1.05 to 1.1 moles, preferably about 1.06 moles, of I per mole of III. The catalyst is used preferably in an amount of 0.05 to 0.1 moles per mole of reactant of the formula I.

The radical X in the compound R^4–X (of the formula I) can be an activated ester such as triflate (trifluoromethane sulfonate), tosylate or mesylate. It can also be a group of the formula —OSO_2F. It should in particular be noted that the process according to the invention could not be carried out on a compound of Formula I wherein X is a halogen atom, even iodine; see the comparative Example, Part B of Example 1 below. This failure clearly distinguishes the present invention from the process described by Ciufolini *et al.*, *J. Org. Chem. [Communications]* **1988**, *53*, 4149-4151, wherein the intramolecular arylation of 'soft' enolates catalyzed by zerovalent palladium is effected by means of an aryl halide.

The process according to the invention is carried out under an inert atmosphere, e.g., argon or nitrogen, and at a convenient temperature and

for a convenient time, e.g., ambient up to about 60°C for 2 to 100 hours, preferably 4 to 50 hours, more preferably 6 to 12 or even 24 hours. The reaction requires an inert aprotic organic solvent such as an ether, e.g. THF or DME, or a hydrocarbon, e.g. an aromatic hydrocarbon such as benzene, or mixtures thereof.

Examples of the strong base include lithium diisopropylamide (LDA) and lithium hexamethyldisilazane (LiHMDS) and the like.

The immediate products of the process according to the invention, namely the α-substituted arylacetamides, may have one or more chirally substituted carbon atoms and therefore may exist in isomeric forms. In particular, compounds of the formula IV (such as (R,S)-1-R^4-1,3,4,5-tetrahydro-2H-3-benzazepin-2-ones), have an asymmetric center at C-1 and can be resolved, e.g. into their (R)- and (S)-forms. However, this resolution can if desired be carried out at a later stage in the preparation of compounds having pharmacological utility.

These immediate products of the reaction, namely the α-substituted arylacetamides, e.g., the compounds of the formula IV (such as (R,S)-1-R^4-1,3,4,5-tetrahydro-2H-3-benzazepin-2-ones) can be used as intermediates in the preparation (by reduction) of α-substituted arylethylamines having pharmacological utility. For example, a 1-R^4-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one can be reduced, preferably with a hydride reducing agent (e.g., in an anhydrous ether solvent with lithium aluminum hydride or with aluminum hydride) to a corresponding 1-substituted-2,3,4,5-tetrahydro-1H-3-benzazepine; further optional steps may also have to be carried out to provide a compound having pharmacological utility, such as the removal of a protecting methyl group from a methoxy substituent (for example, by means of an alkali metal alkylsulfide in an organic aprotic solvent such as DMF, DMSO or DMA, especially sodium ethylsulfide in DMF. The (R)- and (S)-isomers can (if necessary) be separated by known methods at an appropriate point in the synthesis and preferably before the reduction, e.g., by chromatography on a Chiracel OD column with ethanol:hexane (5:95). The product will be a 1-substituted-2,3,4,5-tetrahydro-1H-3-benzazepine having potential pharmacological utility. Compounds in this last-named class include (R)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-

benzazepine (SCH 23390). Other products of the formula IV can if desired be put through these same finishing steps.

Thus the following compounds can be prepared by the novel process of the present invention:

1,3,4,5-Tetrahydro-2H-3-benzazepin-2-ones:

(R,S)-7-chloro-1-(1-cyclohexenyl)-8-methoxy-3-methyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and its (R)- and (S)- isomers;

(R,S)-1-(1-cyclohexenyl)-8-methoxy-3,7-dimethyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and its (R)- and (S)- isomers;

(R,S)-7-chloro-1-(1-cyclopentenyl)-8-methoxy-3-methyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and its (R)- and (S)- isomers;

(R,S)-7-chloro-8-methoxy-3-methyl-(2-methyl-1-cyclopentenyl)-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and its (R)- and (S)- isomers;

(R,S)-7-chloro-8-methoxy-3-methyl-(2-methyl-1-cyclohexenyl)-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and its (R)- and (S)- isomers; and

(R,S)-7-chloro-8-methoxy-3-methyl-1-(1,2-dimethyl-1-propenyl)-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and its (R)- and (S)- isomers.

2,3,4,5-Tetrahydro-1H-3-benzazepines (by reduction and O-demethylation of the (R,S)-compounds listed above):

(R,S)-7-chloro-1-(1-cyclohexenyl)-8-hydroxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, m.p. of hydrobromide 177-179°C;

(R,S)-1-(1-cyclohexenyl)-8-hydroxy-3,7-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepine (as hydrochloride);

(R,S)-7-chloro-1-(1-cyclopentenyl)-8-hydroxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, m.p. of free base 186-188°C;

(R,S)-7-chloro-8-hydroxy-3-methyl-1-(1,2-dimethyl-1-propenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (as hydrochloride);

(R,S)-7-chloro-8-hydroxy-3-methyl-(2-methyl-1-cyclopentenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (as hydrochloride) and

(R,S)-7-chloro-8-hydroxy-3-methyl-(2-methyl-1-cyclohexenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (as hydrochloride).

Resolved enantiomers of 2,3,4,5-tetrahydro-1H-3-benzazepines:

(R)-1-(1-cyclohexenyl)-8-hydroxy-3,7-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepine (as hydrochloride);

(S)-1-(1-cyclohexenyl)-8-hydroxy-3,7-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepine (as hydrochloride);

(R)-7-chloro-1-(1-cyclohexenyl)-8-hydroxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (as hydrochloride);

(S)-7-chloro-1-(1-cyclohexenyl)-8-hydroxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (as hydrochloride);

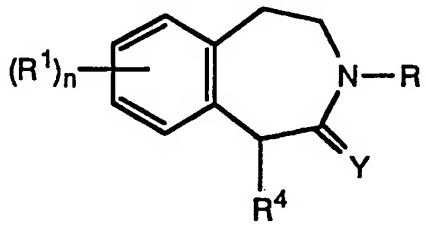
(R)-7-chloro-8-hydroxy-3-methyl-1-(1,2-dimethyl-1-propenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (as hydrochloride);

(S)-7-chloro-8-hydroxy-3-methyl-1-(1,2-dimethyl-1-propenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (as hydrochloride);

(S)-7-chloro-8-hydroxy-3-methyl-(2-methyl-1-cyclopentenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine, m.p. of hydrochloride 248-249°C (dec.); and especially

(R)-7-chloro-8-hydroxy-3-methyl-(2-methyl-1-cyclopentenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine, m.p. of hydrochloride 249-251°C (dec.).

Compounds of the formula



(II);

defined above, and their salts, are novel. Preferred compounds of the formula II include compounds wherein:

n is 1 or 2;

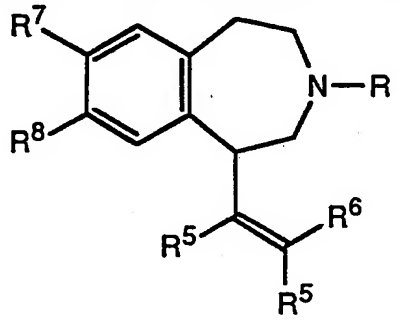
each R^1 is independently selected from lower alkoxy, hydroxy, halogen, polyfluoroloweralkyl, nitro and phenoxy;

R^4 is a 1-cycloalkenyl group;

R is a lower alkyl group;

and Y is H_2.

These compounds have valuable pharmacological properties; for example they have anti-psychotic activity and in particular selectively antagonize the dopamine D-1 receptors. Particularly preferred compounds of the formula II include those of the formula



(IIA);

wherein R is as defined above but is preferably a methyl group;

the two groups R^5 together form a pentamethylene or especially a trimethylene or a tetramethylene group;

R^6 is a lower alkyl group, preferably a methyl group, or a hydrogen atom;

R^7 is selected from lower alkoxy, hydroxy, CF_3 and halogen;

and R^8 is selected from lower alkoxy, hydroxy and halogen;

Preferably, R^7 is halogen and R^8 is hydroxy. Most preferably, R^7 is chlorine.

In particular, the (R)- isomers of the compounds of formula II wherein Y is H_2 and formula IIA are generally preferred to the racemates, and the racemates are generally preferred to the (S)-isomers.

The utility of the compounds of Formula II wherein Y is H_2 may be demonstrated by test procedures designed to indicate their antipsychotic activity.

CONDITIONED AVOIDANCE SUPPRESSION (CAR) IN RATS

Clinically active antipsychotic drugs are known to depress discrete trial avoidance behavior at doses that do not retard the escape response [*Ann. N. Y. Acad. Sci.* 66, 740 (1957)]. A series of experiments was carried out to assess the ability of the compounds of this invention to suppress the conditioned avoidance response (CAR) in rats.

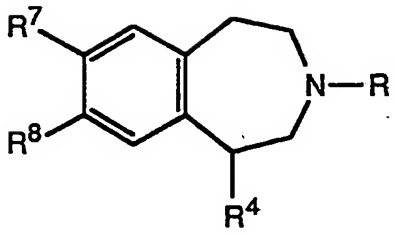
Materials and Methods

Rats were required to jump onto a platform located 6.75 inches (17.15 cm.) above the grid floor of an experimental chamber in response to a 5-second tone to avoid a 10-second foot shock (0.6 ma.). Each experimental session consisted of 20 such trials presented at 30-second intervals. A correct CAR is scored whenever the rat jumps onto the platform during the tone (prior to foot shock). An escape response is scored when the rat jumps onto the platform during a shock. A response failure is defined as the lack of an escape response during the 10-second shock period.

Groups of 6-8 rats were trained in two consecutive days (total of 40 trials). Rats that reached criterion on day 2 (correct CARs in 16 or more of the 20 trials) were treated with either a test drug or a vehicle on day 3. Suppression of CAR was analyzed statistically using Student's t-test comparing the performances of drug-treated to vehicle-treated rats. The minimal effective dose (MED) for each drug is defined as the lowest dose tested that significantly reduced avoidance responses ($P<0.05$).

When tested by the above procedure, representative compounds of the invention and reference compounds showed a dose-related specific blockade of conditioned avoidance response as set forth in Table 1 below:

TABLE 1:



Compound	R^4	R	R^7	R^8	Rat CAR, mg/kg (immediate unless otherwise noted)
A; (±)-(R,S) (Reference)	1-(1-cyclohexenyl)	CH_3	CH_3	OH	>30, po (per oral)
B; (+)-(S) (Reference)	1-(1-cyclohexenyl)	CH_3	CH_3	OH	>30, po
C; (–)-(R) (Reference)	1-(1-cyclohexenyl)	CH_3	CH_3	OH	0.1, sc (sub-cutaneous)
D; (±)-(R,S) (Reference)	1-(1-cyclopentyl)	CH_3	Cl	OH	>30, po; 3, sc
E; (±)-(R,S) (Reference)	1-cyclohexyl	CH_3	CH_3	OH	10, po; 3, sc
G; (±)-(R,S)	1-(2-methyl-1-cyclopentenyl)	CH_3	Cl	OH	10, po; 50, po, at 6 hours; 0.01, sc
H; (–)-(R)	1-(2-methyl-1-cyclopentenyl)	CH_3	Cl	OH	5, po; 25, po, at 6 hours
J; (+)-(S)	1-(2-methyl-1-cyclopentenyl)	CH_3	Cl	OH	>30, po
L; (+)-(S)	1-(1-cyclohexenyl)	CH_3	Cl	OH	>30, po
M; (–)-(R)	1-(1-cyclohexenyl)	CH_3	Cl	OH	10, po
N; (±)-(R,S)	1-(2-methyl-1-cyclohexenyl)	CH_3	Cl	OH	30, po
P; (±)-(R,S)	1-(1,2-dimethyl-1-propenyl)	CH_3	Cl	OH	10, po

SUPPRESSION OF CONDITIONED AVOIDANCE RESPONSE (CAR) IN SQUIRREL MONKEYS

This test is designed to measure the effective duration of activity of candidate compounds.

Male or female squirrel monkeys weighing 800-1200 g housed one per cage are utilized. Initially each monkey is taught to terminate both a 3mA electric shock delivered through the grid floor of the test cage and an overlapping tone by depressing a lever in the cage. The monkeys do not proceed to the second phase of testing unless they depress the lever during the shock component of the trials at least 75% of the time during 60 daily trials on three consecutive days.

In the second phase of the testing, a ten second tone is turned on prior to the shock component. A lever press during the sounding of the tone terminates the tone and prevents the occurrence of the shock component and is denoted as an "avoidance". Compound testing does not begin until the monkey makes at least 85% correct avoidances for five consecutive days.

The compound testing is commenced after three consecutive days of re-testing. The monkey first is injected or orally dosed with the vehicle only and re-tested to show that the vehicle does not affect the response of the monkey. The monkey must achieve at least an 85% correct avoidance before drug testing commences. If this minimal avoidance level is achieved, the next day the monkey is orally dosed or injected with the subject compounds in the appropriate vehicle, and the number of avoidances are recorded. An animal is defined as having been "affected" by any drug treatment if there is a 50% loss of avoidance behavior relative to the performance of the animal when only the vehicle is injected. The minimal effective dose (MED) is defined as that dose producing an effect in at least 50% of the animals.

A test may be conducted to determine the effective duration of activity of a compound in accordance with the present invention by comparing a compound of the invention to the known compound SCH 23390. A compound of the invention administered 60 minutes prior to the test is compared to SCH 23390 administered 30 minutes prior to test. The

duration of activity of each compound is determined by administering a 12.0 mg/kg p.o. dose several hours (*e.g.*, four or six) prior to testing. The ability to decrease significantly the number of avoidances several hours (*e.g.*, four or six) after injection indicates that the compound is still active at that time. Results for representative compounds of the invention and for reference compounds are shown in Table 2 below.

TABLE 2:

Compound	R^4	R	R^7	R^8	Monkey CAR, mg/kg
A; (±)-(R,S) (Reference)	1-(1-cyclo-hexenyl)	CH_3	CH_3	OH	3, po; 10, po, at 1 hour
G; (±)-(R,S)	1-(2-methyl-1-cyclopentenyl)	CH_3	Cl	OH	5, po; 20, po, at 6 hours
H; (–)-(R)	1-(2-methyl-1-cyclopentenyl)	CH_3	Cl	OH	2, po; 10, po, at 4 hours

COMPETITIVE INHIBITION ASSAY

Many compounds capable of effecting reproducible physiological changes in neural tissues are believed to operate by binding at one or more receptor sites. Compounds which interact strongly with these receptor sites in *in vitro* tests, using homogenates of the target organ or structure, are expected to exhibit similar properties when administered *in vivo* and therefore are candidates for continued study as potential therapeutic and/or diagnostic agents.

Binding of a compound to a receptor site, *in vitro*, is demonstrated by the specificity of binding and the saturability of the available sites. A methodology for characterization of binding and an interpretation of the data are described by Billard et al., *Life Sciences* 35, 1885 (1984) in which the binding of (R)-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine (SCH 23390) (as its hemi-maleate) to the dopamine D-1 receptor is characterized.

Materials and Methods

Tritiated SCH 23390 and tritiated spiperone (a potent D-2 ligand) were obtained as described in the Billard et al. reference *supra* and serially diluted in 0.05 M Tris buffer, pH 7.4, as required. A compound of the invention was diluted in 0.05 M Tris buffer, pH 7.4, as required.

Tissue Preparation

Male Sprague-Dawley rats (200 to 250 g) from Charles River Breeding Laboratories, Mass., were used to obtain brain tissue. The rats were humanely sacrificed and their brains removed and placed on ice. Striatal tissue was excised, pooled, and homogenized (Brinkman Polytron, 10 sec) in 100 volumes (w/v) of ice cold 50 mM Tris buffer, pH 7.4 (at 25°C). The homogenate was centrifuged at 20,000 x g for 10 min. The resulting pellet was re-homogenized in Tris buffer and centrifuged again. The final pellet was resuspended in 50 mM Tris buffer, pH 7.4 containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, and 1 mM $MgCl_2$.

Assay

Polypropylene incubation tubes received 100 µl of the individual test compounds at various concentrations dissolved or suspended in 0.05 M Tris buffer, pH 7.4 containing 4 mg/ml methylcellulose, 100 µl of a solution of ^3H-SCH 23390 in Tris buffer (final reaction mixture concentration = 0.3 nM) or 100 µl of a solution of ^3H-spiperone in Tris buffer (final concentration = 0.2 nM) and 800 µl of tissue suspension (ca. 3 mg/assay). Tubes were incubated at 37°C for 15 minutes and rapidly filtered under vacuum through Whatman GF/B filters and rinsed 4 times with 4 ml of ice cold 50 mM Tris buffer, pH 7.4. The filters were transferred to scintillation vials, equilibrated with 10 ml of scintillant (Scintosol, Isolab, Inc.) for 16 hours at 25°C, and the radioactivity was determined in a liquid scintillation counter. K_i values were determined as described by Billard et al. using the relationship: $K_i = IC_{50}/(1 + ([L]/K_D))$ wherein IC_{50} = concentration of test drug necessary to displace 50% of specifically bound ^3H-SCH 23390, [L] = concentration of radioligand used in the assay, and K_D = dissociation constant.

The inhibition constants (K_i) determined from this assay for compounds of the invention and for reference compounds are as shown in Table 3 below:

TABLE 3

Compound	R^4	R	R^7	R^8	K_i (nM) against	
					^{3}H-SCH 23390	^{3}H-spiperone
A; (±)-(R,S) (Reference)	1-(1-cyclohexenyl)	CH_3	CH_3	OH	8.7	1876
B; (+)-(S) (Reference)	1-(1-cyclohexenyl)	CH_3	CH_3	OH	101	4370
C; (–)-(R) (Reference)	1-(1-cyclohexenyl)	CH_3	CH_3	OH	4	1670
D; (±)-(R,S) (Reference)	1-(1-cyclopentyl)	CH_3	Cl	OH	21	1538
E; (±)-(R,S) (Reference)	1-cyclohexyl	CH_3	CH_3	OH	48	3606
F; (–)-(R) (Reference)	1-cyclopentyl	CH_3	CH_3	OH	44	1055
G; (±)-(R,S)	1-(2-methyl-1-cyclopentenyl)	CH_3	Cl	OH	0.27	656
H; (–)-(R)	1-(2-methyl-1-cyclopentenyl)	CH_3	Cl	OH	0.43	358
J; (+)-(S)	1-(2-methyl-1-cyclopentenyl)	CH_3	Cl	OH	15	3694
K; (±)-(R,S)	1-(1-cyclohexenyl)	CH_3	Cl	OH	2.2	1442
L; (+)-(S)	1-(1-cyclohexenyl)	CH_3	Cl	OH	23	2076
M; (–)-(R)	1-(1-cyclohexenyl)	CH_3	Cl	OH	0.87	1087
N; (±)-(R,S)	1-(2-methyl-1-cyclohexenyl)	CH_3	Cl	OH	0.83	420
P; (±)-(R,S)	1-(1,2-dimethyl-1-propenyl)	CH_3	Cl	OH	2.8	554
Q; (±)-(R,S)	1-(1-cyclo-pentenyl)	CH_3	Cl	OH	2.3	595

The comparatively small K_i values of the compounds of the invention in the competitive binding assay with SCH 23390 indicate that the compounds of formula II wherein Y is H_2 bind strongly to the D-1 receptor site. The relatively high K_i values for the D-2 site, for which spiperone is highly selective, indicate that the compounds are not specifically bound to that receptor site.

The compounds of this invention are substantially non-toxic at the therapeutic dose, as is shown in the following Table 4, which compares them with related reference compounds:

TABLE 4: TOXICITY

Compound	R^4	R	R^7	R^8	Toxicity, rat
A; (±)-(R,S) (Reference)	1-(1-cyclo-hexenyl)	CH_3	CH_3	OH	10 mpk po caused salivation in 1 of 3 rats after 1 hour and in 3 of 3 rats after 6 hours
E; (±)-(R,S) (Reference)	1-cyclohexyl	CH_3	CH_3	OH	Lethal at 300 mpk
F; (–)-(R) (Reference)	1-cyclopentyl	CH_3	CH_3	OH	Lethal at 300 mpk
G; (±)-(R,S)	1-(2-methyl-1-cyclopentenyl)	CH_3	Cl	OH	Non-toxic at 300 mpk in the rat
H; (–)-(R)	1-(2-methyl-1-cyclopentenyl)	CH_3	Cl	OH	Non-toxic at 150 mpk in the rat
M; (–)-(R)	1-cyclohexenyl	CH_3	Cl	OH	Secretions at 300 mpk in the rat

The active compounds can be administered orally, transdermally, rectally, or parenterally, for example in the treatment of psychoses. The preferred mode of administration is orally or intravenously.

The compounds of the formula II wherein Y is H_2 or IIA can be administered in conventional oral dosage forms such as capsules, tablets, pills, powders, suspensions or solutions prepared with conventional pharmaceutically acceptable excipients and additives, using conventional techniques. Parenteral preparations, i.e., sterile solutions or suspensions, are also made by conventional means.

Pharmaceutical compositions containing the compounds described by this invention can include solid or liquid inert, pharmaceutically acceptable carriers. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may comprise from about 5 to about 70 percent active ingredient. Suitable solid carriers are known in the art, e.g., magnesium carbonate, magnesium stearate, talc, sugar, and/or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form preparations include solutions, suspensions and emulsions. As an example there may be mentioned water or water-propylene glycol solutions for parenteral injection.

Also included are solid form preparations which are intended for conversion, shortly before use, into liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions. These particular solid form preparations are most conveniently provided in unit dose form and as such are used to provide a single liquid dosage unit. Alternatively, sufficient solid may be provided so that, after conversion into liquid form, multiple individual liquid doses may be obtained by measuring predetermined volumes of the liquid form preparation as with a syringe, teaspoon or other volumetric container. When multiple liquid doses are so prepared, it is preferred to maintain the unused portion of said liquid doses at low temperature (i.e., under refrigeration) in order to retard possible decomposition. The solid form preparations intended for conversion into liquid form may contain flavoring agents, coloring agents, stabilizers, buffers, artificial and natural

sweeteners, dispersing agents, thickeners, solubilizing agents and the like, in addition to the active material. The solvent utilized for preparing the liquid form preparation may be water, isotonic water, ethanol, glycerine, propylene glycol and the like as well as mixtures thereof. Naturally, the solvent utilized will be chosen with regard to the route of administration; for example, liquid preparations containing large amounts of ethanol are not suitable for parenteral use.

The compounds of the invention may also be delivered transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as is conventional in the art for this purpose.

For preparing suppositories, a low-melting wax such as mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into conveniently sized molds, allowed to cool and thereby solidify.

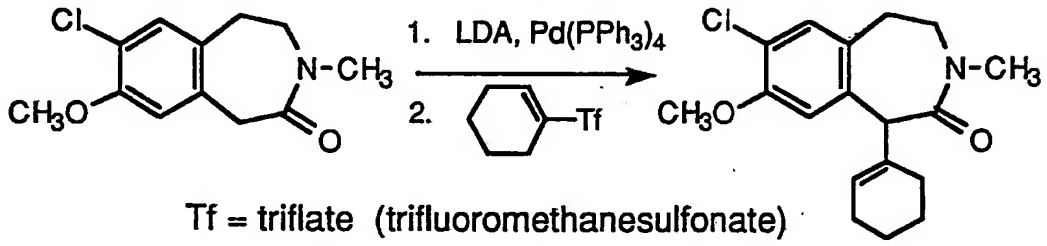
Preferably, the pharmaceutical preparation is in unit dosage form, each unit dose containing an appropriate quantity of the active ingredient, e.g., an effective amount to achieve the desired purpose. The novel compounds are preferably administered at about 0.2 to 10 mg/kg. of body weight. Dosage units preferably contain from 5 to 250 mg, preferably 20 to 100 mg, of active ingredient. A typical daily dosage will be from 10 to 500 mg, preferably from 20 to 250 mg.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small amounts until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions (e.g., two, three or four) during the day if desired.

The following Examples illustrate but do not in any way limit the present invention:

Example 1:

Part A: Preparation of (R,S)-7-Chloro-1-(1-cyclohexenyl)-8-methoxy-3-methyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one



Tf = triflate (trifluoromethanesulfonate)

A mixture of 0.48 g. (2 mmol.) of 7-chloro-8-methoxy-3-methyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one, 0.2.g. (0.17 mmol.) of tetrakis(triphenylphosphine)palladium and 10 ml. of THF was cooled in a dry ice / 2-propanol bath to about -78°C. Under a nitrogen atmosphere, 1.3 ml. of 1.5M lithium diisopropylamide (2 mmol.) in cyclohexane was added through a syringe. The mixture was kept at -78°C for an hour. A solution of 0.50 g. (2.2 mmol.) of 1-cyclohexenyl triflate in 10 ml. of THF was then added. The mixture was allowed to warm to room temperature and stirred for an hour, and then heated for 24 hours at 45°C.

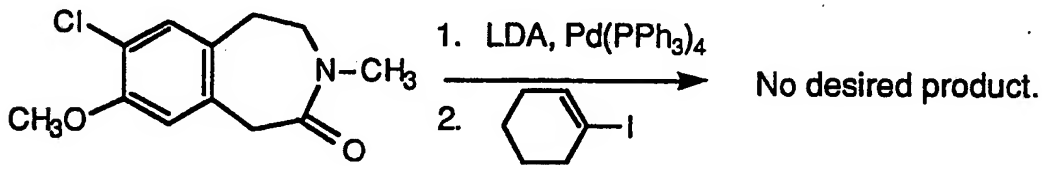
10 ml. of water was added to quench the reaction, and the crude product was extracted with ethyl acetate. Liquid chromatography (flash chromatography using hexane:ethyl acetate 1:1 to 1:4) gave pure (R,S)-7-chloro-1-(1-cyclohexenyl)-8-methoxy-3-methyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one, which was recrystallized from ethyl acetate to provide a white solid (yield 70%), m.p. 126-127°C; thin layer chromatography (TLC): R_f 0.63 (ethyl acetate); ^1H NMR (300 MHz, $CDCl_3$): δ 1.5-1.8 (4H, m), 1.9-2.2 (4H, m), 2.85-3.15 (3H, m), 3.05 (3H, s), 3.89 (3H, s), 4.4 (2H, m), 5.0 (1H, bs), 6.6 (1H, s), 7.15 (1H, s); MS FAB-NBA-DMSO, m/e (%): 322 (39), 320 (MH^+, 100), 292 (7), 290 (9), 239 (11), 212 (6), 210 (15).

The product of Example 1 Part A can be resolved, e.g. by chromatography on a Chiracel column, and then one or both isomers can be reduced. Thus the (R)-isomer will yield (R)-7-chloro-1-(1-cyclohexenyl)-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, which in turn can be demethylated to yield (R)-7-chloro-1-(1-cyclohexenyl)-8-hydroxy-3-

methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, a compound having pharmacological properties. Alternatively, the resolution can be effected at a later stage in the synthesis.

Part B: COMPARATIVE EXAMPLE according to the process described by Ciufolini *et al.*, *J. Org. Chem. [Communications]* **1988**, *53*, 4149-4151.

Attempted Preparation of (R,S)-7-Chloro-1-(1-cyclohexenyl)-8-methoxy-3-methyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one:



No desired product.

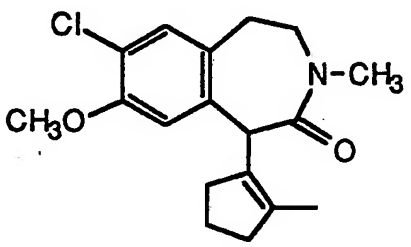
A mixture of 0.75 g. (3.13 mmol.) of 7-chloro-8-methoxy-3-methyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one, 0.3 g. (0.26 mmol.) of tetrakis(triphenylphosphine)palladium and 20 ml. of THF was cooled in a dry ice / 2-propanol bath to about to -78°C. Under a nitrogen atmosphere, 2.1 ml. of 1.5M lithium diisopropylamide in cyclohexane (3.13 mmol.) was added through a syringe with stirring. The mixture was kept at -78°C for an hour. A solution of 0.65 g. (3.13 mmol.) of 1-iodocyclohexene in 10 ml. of THF was then added. The mixture was allowed to warm to room temperature and stirred for an hour, and then heated for 24 hours at 50°C.

The reaction was quenched with 10 ml. of water and then worked up as above in Part A. A complicated mixture was obtained. TLC indicated that most of the starting materials remained. The mixture was separated by liquid chromatography (hexane:ethyl acetate 1:1 to 1:4); no desired product was detected by NMR.

Example 2: Preparation of further arylacetamides.

The following compounds were prepared by the process of Example 1 Part A:

1. (R,S)-7-Chloro-8-methoxy-3-methyl-1-(2-methyl-1-cyclopentenyl)-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one (from 7-chloro-8-methoxy-3-methyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 2-methyl-1-cyclopentenyl-triflate)



Yield 55%; m.p. 120-122°C; TLC (ethyl acetate): R_f 0.67.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 (3H, s), 1.60-1.83 (2H, m), ^{1}H 2.15-2.43 (4H, m), 2.94-3.16 (2H, m), 3.07 (3H, s), 3.17-3.30 (1H, m), 3.87 (3H, s), 4.10-4.25 (1H, m), 4.54 (1H, s), 6.69 (1H, s), 7.14 (1H, s).

MS FAB-NBA-DMSO/CH_2Cl_2, m/e (%): 322 (70), 320 (MH^+, 100), 292 (46), 290 (47), 247 (35), 239 (54), 210 (55), 181 (51), 165 (44), 154 (51).

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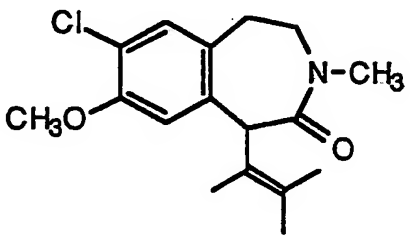
2. (R,S)-7-Chloro-8-methoxy-3-methyl-1-(1,2-dimethyl-1-propenyl)-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one (from 7-chloro-8-methoxy-3-methyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 1,2-dimethyl-1-propenyl-triflate)



Yield 35%; m.p. 125.5-126.5°C; TLC (ethyl acetate): R_f 0.65.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.64 (3H, s), 1.78 (6H, bs), 2.93-3.17 (2H, m), 3.07 (3H, s), 3.42-3.54 (1H, m), 3.80-3.98 (1H, m), 3.89 (3H, s), 4.98 (1H, s), 6.71 (1H, s), 7.15 (1H, s).

MS FAB-G/TG - DMSO, m/e (%): 308 (MH^+, 100), 292 (30), 239 (39), 212 (65), 210 (87).

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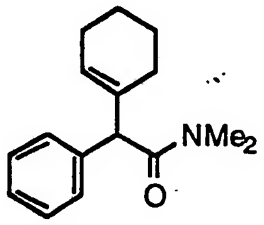
3. (R,S)-α-(1-cyclohexenyl)-N,N-dimethyl-benzeneacetamide (from N,N-dimethyl-benzene-acetamide and 1-cyclohexenyl-triflate)



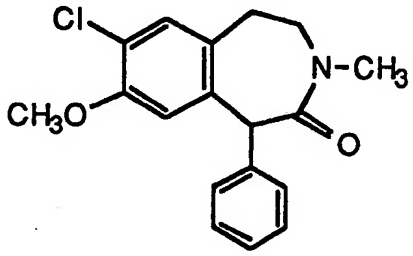
Yield 58%; m.p. 69.5-71.5°C; TLC (ethyl acetate): R_f 0.73.

^1H NMR (300 MHz, $CDCl_3$): δ 1.83-2.01 (1H, m), 2.12-2.28 (1H, m), 2.29-2.45 (1H, m), 2.46-2.61 (1H, m), 3.05 (3H, s), 3.31-3.52 (2H, m), 4.32 (1H, t, j = 7Hz).

MS m/e (%) CI/CH_4: 246 (MH^+, 100), 113 (53).

---

4. (R,S)-7-Chloro-8-methoxy-3-methyl-1-phenyl-1,3,4,5-tetra-hydro-2H-3-benzazepin-2-one (from 7-chloro-8-methoxy-3-methyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and phenyl-triflate)



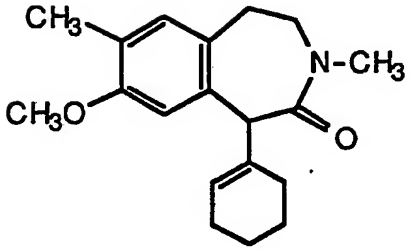
Yield 41%; m.p. 197-198°C; TLC (ethyl acetate): R_f 0.60.

^1H NMR (300 MHz, $CDCl_3$): δ 2.80-3.15 (3H, m), 3.02 (3H, s), 3.60-3.74 (1H, m), 3.86 (3H, s), 5.25 (1H, s), 6.68 (1H, s), 7.22 (1H, s), 7.02-7.35 (5H, m).

MS CI^+/CH_4, m/e (%): 316 (MH^+, 100), 318 (36).

---

5. (R,S)-1-(1-Cyclohexenyl)-8-methoxy-3,7-dimethyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one (from 8-methoxy-3,7-dimethyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 1-cyclohexenyl-triflate)



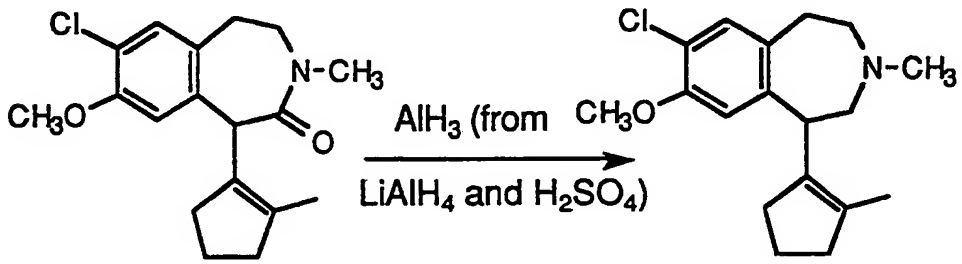
Yield 88%; amorphous solid (no m.p.); TLC (ethyl acetate): R_f 0.67.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.50-1.75 (4H, m), 1.93-2.20 (4H, m), 2.19 (3H, s), 2.83-3.10 (3H, m), 3.05 (3H, s), 3.77 (3H, s), 4.30-4.42 (2H, m), 5.02 (1H, s), 6.46 (1H, s), 6.88 (1H, s).

MS FAB-NBA-DMSO, m/e (%): 300 (MH^+, 100), 299 (77), 298 (48), 272 (13), 270 (20), 241 (18), 227 (15), 219 (20), 190 (29).

\x\bo(\l(Example 3. Preparation of 2,3,4,5-Tetrahydro-1H-3-benzazepines))

Step A: Preparation of (R)-7-Chloro-8-methoxy-3-methyl-(2-methyl-1-cyclopentenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine



Under a nitrogen atmosphere and cooling in an icebath, a solution of 0.2 g of H_2SO_4 (2 mmol) in 10 ml of THF was added to a mixture of 0.23 g of $LiAlH_4$ (6 mmol) and 10 ml of THF. This mixture was allowed to warm to room temperature and kept for an hour. With cooling in an ice-bath, a solution of 1.0 g of the lactam (R)-7-chloro-8-methoxy-3-methyl-(2-methyl-1-cyclopentenyl)-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one (3 mmol) in 10

ml of THF was added through a syringe. The resulting mixture was stirred for 0.5 hour at room temperature.

A mixture of 20 ml of water and 100 ml of THF was added to quench the reaction, and then 10 ml of 5% NaOH was added to precipitate $Al(OH)_3$. This was filtered off, and the filtrate was concentrated on a rotary evaporator. The residue was dissolved in EtOAc and washed twice with water. The organic layer was dried over Na_2SO_4.

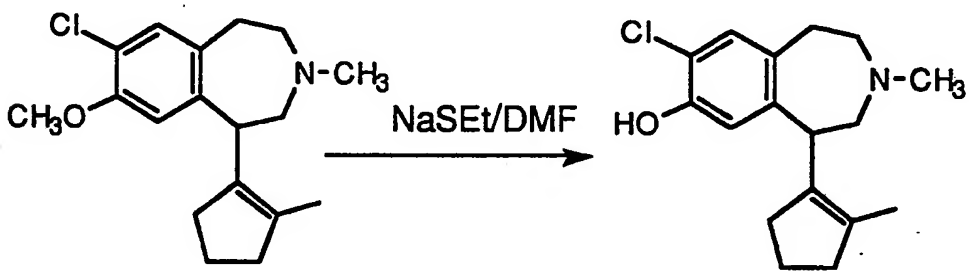
The crude product obtained by distilling off the solvent and drying under vacuum was recrystallized from EtOAc; yield 0.80 g (84%), m.p. 90-91°C.

^1H NMR (300 MHz, $CDCl_3$): δ 1.60 (3H, s), 1.75-2.05 (2H, m), 2.10-2.50 (6H, M), 2.40 (3H, s), 2.66-3.24 (4H, m), 3.80 (3H, s), 4.00-4.10 (1H, d), 6.62 (1H, s), 7.11 (1H, s).

MS FAB-NBA-DMSO, m/e (%): 306 (MH^+, 100), 212 (21), 210 (44.5), 197 (23).

Anal.: Calcd. for $C_{18}H_{24}ClNO$: C 70.69, H 7.91, N 4.58, Cl 11.59; Found: C 70.89, H 7.86, N 4.70, Cl 11.59.

Step B: Preparation of (R)-7-Chloro-8-hydroxy-3-methyl-(2-methyl-1-cyclopentenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine



A mixture of 3.10 g of (R)-7-chloro-8-methoxy-3-methyl-(2-methyl-1-cyclopentenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (10 mmol), 6 g of NaSEt (67 mmol) and 50 ml of DMF was heated at 140°C for 6 hours, and then cooled to room temperature. Some acetic acid was added to pH 7-8, and then 25 ml of EtOH and 25 ml of saturated $NaHCO_3$ solution were added. This mixture was heated under house vacuum (a few cm Hg) at 80°C to remove volatile mercaptan and solvent. The residue was dissolved in EtOAc and the solution was washed with water twice; the organic layer was dried over Na_2SO_4.

This solution was concentrated on a rotary evaporator, and the residue was recrystallized from EtOAc to yield an off-white solid, 2.14 g (72%), m.p. 186-187 (dec.). It was further recrystallized from EtOAc, m.p. 189-190 (dec.).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60 (3H, s), 1.82-2.00 (2H, m), 2.20-2.55 (6H, m), 2.55 (3H, s), 2.70-3.32 (4H, m), 4.05-4.18 (1H, d), 6.68 (1H, s), 7.10 (1H, s).

MS m/e (%) CI^+/CH_4: 292 (MH^+, 100), 258 (19); (EI) 291 (M, 19%), 219 (8), 183 (13), 136 (18).

Anal.: Calcd. for $C_{17}H_{22}ClNO$: C 69.97, H 7.60, N 4.80, Cl 12.15; found: C 69.94, H 7.47, N 4.85, Cl 11.89.

High resolution MS: Calcd for $C_{17}H_{23}ClNO^+$ (MH^+): 292.1468; found: 292.1461.

This free base was dissolved in EtOAc, and a solution of HCl in Et_2O was added to pH~3 to precipitate the white HCl salt, which was filtered off and washed twice with ether; yield (dry): 1.97 g, m.p. 263°C (dec.).

^{1}H NMR (300 MHz, DMSO): δ 1.15 (3H, s), 1.8-2.1 (2H, m), 2.22-2.55 (4H, m), 2.80 (3H, s), 2.7-3.25 (4H, m), 3.25-3.7 (4H, m), 4.35-4.62 (1H, d), 6.70 (1H, s), 7.22 (1H, s).

Anal.: Calcd. for $C_{17}H_{23}Cl_2NO$: C 62.20, H 7.06, N 4.27, Cl 21.60; found: C 62.32, H 7.00, N 4.33, Cl 21.16.

The following compounds can also be prepared by the novel process of the present invention, especially by the processes exemplified in the foregoing Examples:

1,3,4,5-Tetrahydro-2H-3-benzazepin-2-ones:

(R,S)-7-chloro-1-(1-cyclohexenyl)-8-methoxy-3-methyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and its (R)- and (S)- isomers;

(R,S)-1-(1-cyclohexenyl)-8-methoxy-3,7-dimethyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and its (R)- and (S)- isomers;

(R,S)-7-chloro-1-(1-cyclopentenyl)-8-methoxy-3-methyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and its (R)- and (S)- isomers;

(R,S)-7-chloro-8-methoxy-3-methyl-(2-methyl-1-cyclopentenyl)-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and its (R)- and (S)- isomers;

(R,S)-7-chloro-8-methoxy-3-methyl-(2-methyl-1-cyclohexenyl)-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and its (R)- and (S)- isomers; and

(R,S)-7-chloro-8-methoxy-3-methyl-1-(1,2-dimethyl-1-propenyl)-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and its (R)- and (S)- isomers.

2,3,4,5-Tetrahydro-1H-3-benzazepines (by reduction and demethylation of the compounds listed above):

(R,S)-7-chloro-1-(1-cyclohexenyl)-8-hydroxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, m.p. of hydrobromide 177-179°C;

(R,S)-1-(1-cyclohexenyl)-8-hydroxy-3,7-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepine (as hydrochloride);

(R,S)-7-chloro-1-(1-cyclopentenyl)-8-hydroxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, m.p. of free base 186-188°C;

(R,S)-7-chloro-8-hydroxy-3-methyl-(2-methyl-1-cyclopentenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (as hydrochloride);

(R,S)-7-chloro-8-hydroxy-3-methyl-1-(1,2-dimethyl-1-propenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (as hydrochloride); and

(R,S)-7-chloro-8-hydroxy-3-methyl-(2-methyl-1-cyclohexenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (as hydrochloride).

Resolved enantiomers of 2,3,4,5-tetrahydro-1H-3-benzazepines:

(R)-1-(1-cyclohexenyl)-8-hydroxy-3,7-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepine (as hydrochloride);

(S)-1-(1-cyclohexenyl)-8-hydroxy-3,7-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepine (as hydrochloride);

(R)-7-chloro-1-(1-cyclohexenyl)-8-hydroxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (as hydrochloride);

(S)-7-chloro-1-(1-cyclohexenyl)-8-hydroxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (as hydrochloride);

(R)-7-chloro-8-hydroxy-3-methyl-(2-methyl-1-cyclopentenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine, m.p. of hydrochloride 249-251°C (dec.);

(S)-7-chloro-8-hydroxy-3-methyl-(2-methyl-1-cyclopentenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine, m.p. of hydrochloride 249-251°C (dec.);

(R)-7-chloro-8-hydroxy-3-methyl-1-(1,2-dimethyl-1-propenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (as hydrochloride);

(S)-7-chloro-8-hydroxy-3-methyl-1-(1,2-dimethyl-1-propenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (as hydrochloride);

(R)-7-chloro-8-hydroxy-3-methyl-(2-methyl-1-cyclopentenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine, m.p. of hydrochloride 248-249°C (dec.); and

(S)-7-chloro-8-hydroxy-3-methyl-(2-methyl-1-cyclopentenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine, m.p. of hydrochloride 248-249°C (dec.).

Also:

(R)-7-chloro-8-hydroxy-3-methyl-1-phenyl 2,3,4,5-tetrahydro-1H-3-benzazepine (SCH 23390).

The descriptions of the foregoing embodiments of the invention have been presented for purpose of illustration and description. They are not intended to be exhaustive or to limit the invention to the precise forms disclosed, and obviously many modifications and variations are possible in light of the above teaching. The embodiments were chosen and described in order to explain the principles of the invention clearly and thereby enable others skilled in the art to utilize the invention in the best mode possible and in various embodiments and with various modifications such as are suited to the particular use contemplated. The scope of the invention is defined only by the claims appended hereto.

WE CLAIM:

1. A process for the preparation of α-substituted arylacetamides wherein the substituent is an aromatic or aromatic heterocyclic group or a 1-alkenyl or 1-cycloalkenyl group and wherein the nitrogen atom carries no hydrogen atoms;

which comprises the reaction of an arylacetamide having one or two hydrogen atoms on the α-carbon atom, wherein the nitrogen atom carries no hydrogen atoms, with a strong base in an inert aprotic organic solvent;

followed by reaction, in the presence of a zerovalent transition metal catalyst, with a compound of the formula

$$R^4–X \qquad (I),$$

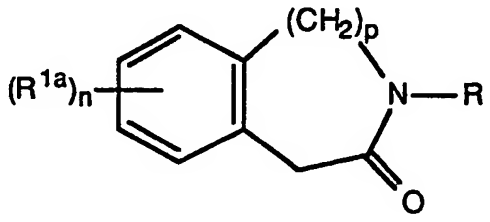
wherein R^4 is selected from aromatic groups, 1-alkenyl groups and 1-cycloalkenyl groups;

and X is a leaving group.

2. A process as claimed in claim 1 wherein the arylacetamide is α-unsubstituted and its amide function forms a fused ring with the aryl group.

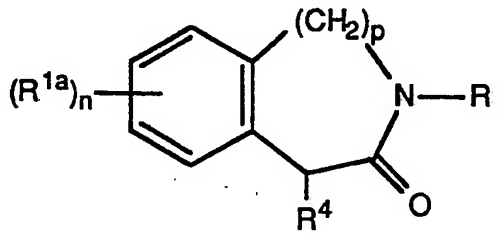
3. A process as claimed in claim 2 wherein the α-unsubstituted arylacetamide is a 3-unsubstituted 1,3-dihydro-2H-indol-2-one, 4-unsubstituted 1,2,3,4-tetrahydro-isoquinolin-3-one, a 1-unsubstituted 1,3,4,5-tetrahydro-2H-3-benzazepin-2-one or a 1-unsubstituted 1,2,3,4,5,6-hexahydro-3-benzazocin-2-one.

4. A process as claimed in claim 3 wherein the α-unsubstituted arylacetamide has the formula:



(III),

and yields a 3-substituted 1,3-dihydro-2H-indol-2-one, 4-substituted 1,2,3,4-tetrahydro-isoquinolin-3-one, 1-substituted 1,3,4,5-tetrahydro-2H-3-benzazepin-2-one or 1-substituted 1,2,3,4,5,6-hexahydro-3-benzazocin-2-one of the formula



(IV);

wherein p is 0, 1, 2 or 3;

n is 0, 1, 2, 3 or 4;

each R^{1a} is independently selected from alkyl, alkenyl, alkoxy, alkenyloxy, cycloalkyl, nitro, halogen, polyfluoroloweralkyl, or phenyl or phenoxy, or two groups R^{1a} in adjacent positions can form an alkylenedioxy group or a fused benzene ring, and the phenyl or phenoxy group or the fused benzene ring is optionally substituted by a group selected from alkyl, alkenyl, alkoxy, alkenyloxy, cycloalkyl, nitro, halogen, polyfluoroloweralkyl, and alkylenedioxy;

R^4 is selected from aromatic groups, 1-alkenyl groups and 1-cycloalkenyl groups;

and R is an alkyl, alkenyl, aryl, aralkyl, cycloalkyl or cycloalkylalkyl group.

5. A process as claimed in claim 1 wherein the zerovalent transition metal catalyst has the formula $M[L]_4$, wherein M is palladium or nickel and L is a trisubstituted phosphine serving as a ligand.

6. A process as claimed in claim 5 wherein the palladium-containing or nickel-containing catalyst is selected from tetrakis(triphenylphosphine)-palladium(0), tetrakis(triphenylphosphine)-nickel(0), tetrakis[tri(furanyl-2)phosphine]-palladium(0), and tetrakis[tri(furanyl-2)]phosphine)-nickel(0).

7. A process as claimed in claim 5 wherein the palladium-containing or nickel-containing catalyst is used in an amount of 0.05 to 0.1 moles per mole of reactant of the formula I.

8. A process as claimed in claim 1 wherein the strong base is lithium diisopropylamide or lithium hexamethyldisilazane.

9. A process for the preparation of α-substituted arylethylamines wherein the substituent is an aromatic group or a 1-alkenyl or 1-cycloalkenyl group and wherein the nitrogen atom carries no hydrogen atoms;

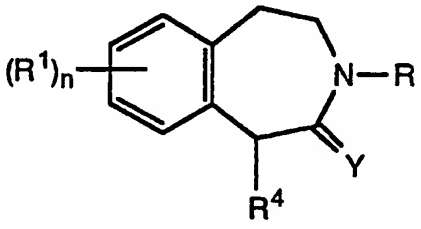
which comprises the reaction of an arylacetamide having at least one hydrogen atom on the α-carbon atom, wherein the nitrogen atom carries no hydrogen atoms, with a strong base in an inert aprotic organic solvent;

followed by reaction, in the presence of a zerovalent transition metal catalyst, with a compound of the formula R^4–X, wherein R^4 is selected from aromatic groups, 1-alkenyl groups and 1-cycloalkenyl groups, and X is a leaving group,

and then by reduction of the so-formed α-substituted arylacetamide to an α-substituted arylethylamine.

10. A process as claimed in claim 9 wherein the α-substituted arylethylamine carries a methoxy substituent in its aryl group and the step of reduction is followed by a step of demethylation of said methoxy substituent to a hydroxy group.

11. Compounds of the formula



(II);

wherein

n is 0, 1, 2, 3 or 4;

each R^1 is independently selected from alkenyl, alkoxy, hydroxy, alkenyloxy, cycloalkyl, nitro, halogen, polyfluoroloweralkyl, phenyl and phenoxy, or two groups R^1 in adjacent positions optionally form an alkylenedioxy group or a fused benzene ring, and the phenyl or phenoxy group or the fused benzene ring is optionally substituted by a group selected from alkyl, alkenyl, alkoxy, hydroxy, alkenyloxy, cycloalkyl, nitro, halogen, polyfluoroloweralkyl, and alkylenedioxy;

R^4 is a 1-cycloalkenyl group;

R is an alkyl, alkenyl, aryl, aralkyl, cycloalkyl or cycloalkylalkyl group;

and Y is an oxygen atom or H_2;

and their non-toxic salts with bases when R^1 is or contains a hydroxy group;

and their non-toxic acid addition salts.

12. Compounds of the formula II defined in claim 11 wherein:

n is 1 or 2;

each R^1 is independently selected from lower alkoxy, hydroxy, halogen, nitro and phenoxy;

R^4 is a 1-cycloalkenyl group;

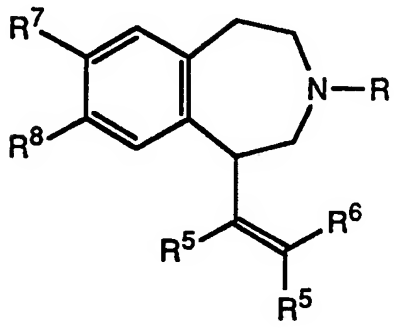
R is a lower alkyl group;

and Y is H_2;

and their non-toxic salts with bases when R^1 is or contains a hydroxy group;

and their non-toxic acid addition salts.

13. Compounds as claimed in claim 11 having the formula



(IIA);

wherein R is as defined in claim 11;

the two groups R^5 together form a pentamethylene, a trimethylene or a tetramethylene group;

R^6 is a lower alkyl group or a hydrogen atom;

R^7 is selected from lower alkoxy, hydroxy, CF_3 and halogen;

and R^8 is selected from lower alkoxy, hydroxy and halogen;

and their non-toxic salts with bases;

and their non-toxic acid addition salts.

14. Compounds and salts as claimed in claim 13 wherein

R is a methyl group;

the two groups R^5 together form a trimethylene or a tetramethylene group;

R^7 is halogen and R^8 is hydroxy.

15. Compounds and salts as claimed in claim 14 wherein R^7 is methyl or chlorine.

16. Compounds as claimed in claim 11, namely:

(R,S)-7-chloro-1-(1-cyclohexenyl)-8-methoxy-3-methyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and its (R)- and (S)- isomers;

(R,S)-1-(1-cyclohexenyl)-8-methoxy-3,7-dimethyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and its (R)- and (S)- isomers;

(R,S)-7-chloro-1-(1-cyclopentenyl)-8-methoxy-3-methyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and its (R)- and (S)- isomers;

(R,S)-7-chloro-8-methoxy-3-methyl-(2-methyl-1-cyclopentenyl)-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and its (R)- and (S)- isomers;

(R,S)-7-chloro-8-methoxy-3-methyl-(2-methyl-1-cyclohexenyl)-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and its (R)- and (S)- isomers; and

(R,S)-7-chloro-8-methoxy-3-methyl-1-(1,2-dimethyl-1-propenyl)-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and its (R)- and (S)- isomers.

17. Compounds as claimed in claim 13, namely:

(R,S)-7-chloro-1-(1-cyclohexenyl)-8-hydroxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine;

(R,S)-1-(1-cyclohexenyl)-8-hydroxy-3,7-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepine;

(R,S)-7-chloro-1-(1-cyclopentenyl)-8-hydroxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine;

(R,S)-7-chloro-8-hydroxy-3-methyl-(2-methyl-1-cyclopentenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine;

(R,S)-7-chloro-8-hydroxy-3-methyl-1-(1,2-dimethyl-1-propenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine; and

(R,S)-7-chloro-8-hydroxy-3-methyl-(2-methyl-1-cyclohexenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine.

18. Compounds as claimed in claim 13, namely:

(R)-1-(1-Cyclohexenyl)-8-hydroxy-3,7-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepine;

(S)-1-(1-cyclohexenyl)-8-hydroxy-3,7-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepine;

(R)-7-chloro-1-(1-cyclohexenyl)-8-hydroxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine;

(S)-7-chloro-1-(1-cyclohexenyl)-8-hydroxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine;

(R)-7-chloro-8-hydroxy-3-methyl-1-(1,2-dimethyl-1-propenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine;

(S)-7-chloro-8-hydroxy-3-methyl-1-(1,2-dimethyl-1-propenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine;

(R)-7-chloro-8-hydroxy-3-methyl-(2-methyl-1-cyclopentenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine; and

(S)-7-chloro-8-hydroxy-3-methyl-(2-methyl-1-cyclopentenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine.

19. A compound as claimed in claim 13, namely:
(R)-7-Chloro-8-hydroxy-3-methyl-(2-methyl-1-cyclopentenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine.

20. Salts as claimed in claim 11 formed with hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, or methanesulfonic acid.

21. Salts as claimed in claim 11 in the form of their sodium, potassium or calcium salts.

22. A method of treating a patient suffering from psychoses, comprising the administration to said patient of an effective amount of a compound as claimed in claim 11.

23. A pharmaceutical composition, especially for treating psychoses, comprising a compound as claimed in claim 11 in association with a pharmaceutically acceptable carrier or excipient.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 93/01425

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D223/16; C07D217/24; C07D209/34; A61K31/55
C07D223/16

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
Y	WO,A,9 119 698 (SCHERING CORPORATION) 26 December 1991 cited in the application see page 6 - page 23; claims; example 17 ---	1,2, 4-11,23
Y	EP,A,0 285 919 (SCHERING CORPORATION) 12 October 1988 cited in the application see page 10 - page 44 ---	1,2, 4-11,23
Y	JOURNAL OF ORGANIC CHEMISTRY. vol. 53, 1988, EASTON US pages 4149 - 4151 M. CIUFOLINI 'INTRAMOLECULAR ARYLATIONS OF SOFT ENOLATES CATALYSED BY ZEROVALENT PALLADIUM' cited in the application see page 4150 - page 4151 --- -/--	1,2,4-10

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
14 MAY 1993	25.05.93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	FRANCOIS J.C.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	JOURNAL OF ORGANIC CHEMISTRY. vol. 55, 1990, EASTON US pages 3454 - 3455 E.PEARS ET AL. 'A NEW 5-MEMBERED RING ANNULATION METHOD BASED ON PD(0)-CATALYSED INTRAMOLECULAR COUPLING OF VINYL IODIDE AND ENOLATE ANION FUNCTIONS.' cited in the application see page 3454 - page 3455	1,2,4-11

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/US93/01425

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 22 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the attributed effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9301425
SA 70592

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 14/05/93

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9119698	26-12-91	AU-A-	8201591	07-01-92
EP-A-0285919	12-10-88	AU-B-	619744	06-02-92
		AU-A-	1596488	02-11-88
		EP-A-	0357641	14-03-90
		JP-T-	2502723	30-08-90
		WO-A-	8807526	06-10-88
		US-A-	5015639	14-05-91